Development and in-vitro evaluation of a colon-specific controlled release drug delivery system

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Abstract
The major challenges in targeting drug to various parts of the gastrointestinal tract include control of drug release with respect to its environment and transit time. These two variables should be taken into consideration in designing a rational colonic drug delivery system. To this end, a swelling matrix core containing pectin, hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose and 5-aminosalicylic acid was developed. This was subjected to a dual coating operation: an inner pH-sensitive enteric and an outer semi-permeable membrane coat with a pore former. In-vitro dissolution studies were carried out in USP apparatus-I using sequential pH media. The first 2 h of dissolution studies were done in HCl buffer at pH 1.5, the next 2 h in pH 5.5 and, finally, in phosphate buffer at pH 6.8 with and without pectinolytic enzyme present. Less than 2% drug was released in the first 6 h and about 90% released in the following 12 h in a controlled manner. The stability studies of the coated systems were performed for 90 days under various conditions and it was found that drug release was not adversely affected. Results indicate that this delivery system has potential for site-specific delivery of drugs to the colon irrespective of transit time and rapid changes in the proximal pH of the gastrointestinal tract.

Introduction
Colon-specific drug delivery systems based on pH sensitivity, biodegradable polymers or prodrugs intended for local or systemic effects have been investigated in the past. The advantages of delivering drug to the colon for topical effects include reduction of incidence of systemic side effects and greater localized drug concentrations in the inflamed or diseased tissues (Tozar et al 1995). Furthermore, in many cases drug dose can be reduced, as the drug is delivered directly, and in its intact form, to the target site. For example, a disease like ulcerative colitis can effectively be treated by local delivery of low doses of specific active agents (Rubinstein 1990; Friend 1991). Additionally, the neutral pH of around 7 ± 0.3, long residence time, and relatively lower proteolytic enzyme activity in the colon may be advantageous for delivering drugs that are degraded or poorly absorbed in the upper gastrointestinal tract, such as peptides, protein-based drugs, calcitonin, vasopressin, etc. (Saffran et al 1986; Antonin et al 1992). Moreover, drug delivery with particular release modulation (chronotherapy) for the treatment of certain diseases can be achieved by delivering drugs to the distal gastrointestinal environment (Youan 2004).

The major challenges of colonic drug delivery are related to the physiological constraints, as the gastrointestinal ecosystem is a complex one. The presence of a variety of microorganisms and their enzyme systems are, in part, responsible for its metabolic diversity (Moore & Holdeman 1975; Gustafsson 1982). Like many physiological parameters, gastrointestinal pH is influenced by various factors including diet, disease, presence of gases, fatty acids and other fermentation products (Rubinstein 1990). In addition, gastric residence time is highly variable. Various factors, such as the quality and quantity of the food present in the stomach, disease, age and emotional status of the patient, are responsible for causing inter- as well as intra-subject variability in gastric transit time, which can result in unpredictable outcome from the dosage form. Nevertheless, under ordinary circumstances, the gastric transit time of non-disintegrating tablets is considered to be a few hours (e.g. 2 ± 1 h) and the small intestinal transit time is generally about 3–4 h (Kaus & Fell 1984; Davis et al 1986; Coupe et al 1991; Reddy et al 1999).
Over the past two decades considerable effort has been made in designing and developing colonic delivery systems and they have been discussed in a number of recent reviews (Chourasia & Jain 2003; Basit 2005; Van den Mooter 2006). In developing colon-specific delivery systems, two different approaches for drug release activation have been adopted: time-dependent and environment-dependent systems. The time-dependent system refers to one that releases the active ingredient after a specified time following ingestion of the system, which may conform with transit time to the colon (Theeuwes et al 1990; Pozzi et al 1994). Due to highly unpredictable gastric transit time, prediction of the drug release location is not always reliable from this kind of delivery system.

The environment-dependent system refers to one that releases drug due to collapse or degradation of the system by the colonic or certain gastrointestinal environment. Exploitation of the colonic environment, thus, involves its pH, or its microbial population with significant enzymatic activity. Colonic microflora-mediated drug release has been utilized to develop prodrugs. Two basic approaches have been employed in delivering drug to the colon by using the prodrug technique: release of the active drug is triggered by azo-reduction or by hydrolysis of glycosides (Friend 1991). However, a prodrug is considered to be a new compound and its safety and efficacy have to be established beforehand. The pH-dependent drug delivery systems include the use of enteric coating materials such as Eudragit L, Eudragit S and cellulose acetate phthalate. Because of inter- and intra-subject variability in gastrointestinal transit time and pH, systems with a pH-dependent polymer alone often result in unpredictable drug release (Ashford et al 1993).

The objective of this project was to develop a colonic drug delivery system with controlled onset and release rate satisfying both temporal and spatial constraints using 5-amino salicylic acid (5-ASA) as the model drug. In this context, dual-coated matrix tablets were developed with the aim that the drug release should begin at least 6–8 h after ingestion of the dosage form; and the drug release should take place in a controlled release manner with complete delivery. To impart some degree of site specificity to the delivery system, pectin (low methoxylated) was incorporated in the formulations. Pectin is a non-toxic soluble complex carbohydrate degraded by colonic bacterial pectinolytic enzymes. In addition, HPMC (E4MP) was used in the formulations as a release modulator to develop a controlled release system.

Preparation of core tablets
Six different formulations were evaluated initially with the aim of selecting the most suitable one for further development (Table 1). A 500-g batch was processed by wet granulating method using 5% aqueous solution of HPMC (E15LVP) as the granulating agent. Tablets were manufactured in a Stokes 16-punch rotary tablet machine (Stokes Inc., Philadelphia, PA) with an average weight of 410 mg (± 6) using an 11-mm concave shaped die and punches.

Coating of the core tablets
To achieve the goals of this project, two layers of coat were applied on the core tablets: the inner enteric coat with cellulose acetate phthalate (CPD) and the outer semipermeable film of ethylcellulose dispersions. The CPD was plasticized with 19% (w/w in relation to polymer contents) triethyl citrate. Surelease-E-7-7050 was supplied as plasticized with dibutyl sebacate (Surelease-E-7-7050) was provided by Colorcon (West point, PA). Samples of triethyl citrate (TEC) were provided by Morflex (Greensboro, NC). Polyethylene glycol (PEG; Carbowax 1450) was given by Union Caribide (Danbury, CT). Preval spray gun and hot-air blower were obtained from local hardware stores.

Table 1 Core formulations and their dissolution data at pH 6.8 without enzymes

<table>
<thead>
<tr>
<th>Formulation</th>
<th>5-ASA (mg)</th>
<th>Pectin (mg)</th>
<th>Avicel (mg)</th>
<th>HPMC (mg)</th>
<th>Hardness (kp)</th>
<th>T-10 (h)</th>
<th>T-50 (h)</th>
<th>T-90 (h)</th>
<th>MDT-10 (h)</th>
<th>MDT-50 (h)</th>
<th>MDT-90 (h)</th>
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<tr>
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<td>100</td>
<td>200</td>
<td>0</td>
<td>100</td>
<td>8.6 ± 3.2</td>
<td>1.9 ± 0.8</td>
<td>7.8 ± 1.1</td>
<td>17.6 ± 1.3</td>
<td>2.4 ± 0.5</td>
<td>9.2 ± 1.1</td>
<td>18.1 ± 1.2</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>0</td>
<td>200</td>
<td>100</td>
<td>16.6 ± 1.4</td>
<td>1.2 ± 0.6</td>
<td>5.8 ± 0.8</td>
<td>11.2 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>7.3 ± 0.9</td>
<td>12.6 ± 1.1</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>11.6 ± 2.1</td>
<td>1.5 ± 0.5</td>
<td>6.6 ± 1.4</td>
<td>15.3 ± 0.8</td>
<td>2.3 ± 0.7</td>
<td>7.9 ± 0.8</td>
<td>16.4 ± 0.9</td>
</tr>
<tr>
<td>D</td>
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<td>100</td>
<td>150</td>
<td>50</td>
<td>10.8 ± 2.3</td>
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<td>200</td>
<td>50</td>
<td>15.3 ± 2.2</td>
<td>0.6 ± 0.5</td>
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<td>6.1 ± 0.6</td>
<td>1.4 ± 0.5</td>
<td>3.8 ± 0.7</td>
<td>6.8 ± 0.7</td>
</tr>
<tr>
<td>F</td>
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<td>50</td>
<td>225</td>
<td>25</td>
<td>14.8 ± 1.8</td>
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<td>1.1 ± 0.4</td>
<td>3.1 ± 0.6</td>
<td>5.3 ± 0.5</td>
</tr>
</tbody>
</table>

T-10, T-50 and T-90 refer to time taken to release 10%, 50% and 90% of the contents; MDT, mean dissolution time. Data are presented as means ± s.d., n = 6.
A 12-inch Erweka AR-400 (Heusenstamm, Germany) coating pan was used for coating the tablets. A Preval spray gun was calibrated to deliver 2–3 g min⁻¹ of the composition with manual sequential actuations of the device. The inlet temperature of 60–70°C was maintained while the bed temperature was about 35–45°C and pan speed was set at 15 rev min⁻¹ to avoid sticking of the tablets. The tablet bed was pre-warmed for about 10 min and the tablets were coated to different weight gains (e.g. 2.5%, 5%, 7.5% and 10%) with respect to the initial tablet weight. For multiple coats, Aquacoat-CPD was applied first, and Surelease alone or with channelling agent was applied on top of the first coat. After gaining the desired weight, the tablets were left in the rotating warm pan for about 10 min for further drying. The coated 5-ASA tablets were placed in glass vials and allowed to equilibrate to ambient environment for 14 days before conducting in-vitro evaluation.

**In-vitro release studies**

For preliminary screening purposes, dissolution studies of core tablets were carried out in USP apparatus-I (basket) at 50 rev min⁻¹ using 900 mL USP phosphate buffer at pH 6.8 and 37°C (± 0.5) in a Vankel (VK7000) dissolution apparatus (Varian, NC) equipped with fully automated 7-channel peristaltic pump and HP-8453 diode array spectrophotometer. To evaluate the effects of pectinolytic enzymes on the matrix containing pectin, separate dissolutions were carried out with 3 mL of enzymes in the media.

Once the promising coated formulation was identified (onset of drug release in about 6 h and over 80% release taking place in about 18 h), media with a sequential pH gradient containing pectinolytic enzymes were employed for further dissolution studies. For the first 2 h dissolution was carried out in 900 mL media at pH 1.5. The tablets were then transferred to media having pH 5.5 for a further 2 h, followed by pH 6.8 with 3 mL of pectinolytic enzymes. In addition, dissolutions were carried out in media of pH 1.5 and 5.5 to investigate the effect of low pH on drug release.

**Stability of dual-coated tablets**

The tablets were stored under different conditions: sealed glass bottle without desiccant; sealed glass bottle with silica gel as desiccant; and open glass container. To perform accelerated stability at 40°C and 75% relative humidity, samples were placed in a sealed jar containing saturated sodium chloride solution and placed in a water bath (Nyqvist 1983). After 90 days the samples were subjected to dissolution studies in USP phosphate buffer at pH 6.8 to verify whether any changes in dissolution profiles took place due to stability issues.

**Dissolution data treatment**

For interpretation and comparison of dissolution data derived from different formulations, the time taken for x% drug release (T-x), mean dissolution time (MDT%) and the similarity factor, f₂, were utilised. In the time-point approach the T-10, T-50 and T-90 values as well as MDT-10, MDT-50 and MDT-90 were calculated for each formulation. The MDT is defined as the sum of different release fraction periods (release areas) during dissolution studies divided by the initial loading dose and is calculated by the following equation (Kim & Fassihi 1997):

\[
\text{MDT} = \frac{\sum_{i=1}^{n} t_i M_i}{M_{\infty}}
\]

where \( M_i \) is the fraction of dose released in time \( t_i = (t_i + t_{i-1})/2 \) and \( M_{\infty} \) is the total amount of drug released (i.e. the loading dose).

In the pair-wise approach, determination of a difference factor, \( f_1 \), and similarity factor, \( f_2 \), using the mean percentage released values were performed by using the following equations (Moore & Flanner 1996; Pillay & Fassihi 1998):

\[
f_1 = \left( \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right) \times 100\%
\]

\[
f_2 = 50 \log \left\{ 1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right\}^{0.5} \times 100
\]

where \( n \) is the number of pull points, \( w_t \) is a weight factor, \( R_t \) is the reference assay at time point \( t \) and \( T_t \) is the test assay at time point \( t \). \( f_1 \) is an approximation of the percentage of error between two profiles. The percent error approaches to zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the profiles. The value of similarity factor, \( f_2 \), ranges between 50 and 100. When the test and reference profiles are identical, \( f_2 \) value approaches to 100, and as the value decreases, the dissimilarity between the profiles increases.

**Results and Discussion**

**Release of 5-ASA from uncoated (core) tablets**

From the dissolution data of the core tablets it appears that formulation F is the most appropriate one to achieve the goals of this project, as 90% of drug release took place in about 4 h in pH 6.8 buffer. Moreover, the MDT-10, MDT-50 and MDT-90 for that formulation was calculated to be 1.1, 3.1 and 5.3, respectively (Table 1). The rationale for using that formulation for further development was that the combined transit times in the ascending and transverse colon is about 7 h for patients with ulcerative colitis, and for non-diseased colon it is about 17 h (Hardy et al 1988). Since the tablets would be subjected to a double coat, it was expected that the overall release time would be longer and would satisfy the objectives of this work.

**Dissolution of coated tablets**

Times to release 10%, 50% and 90% (T-10, T-50 and T-90) of the drug from the coated tablets as a function of coating weight
At 2.5% weight gain with Surelease alone about 80% drug release took place in about 24 h, while at 5% weight gain only about 22% was released. At a low level of coating (2.5% weight gain), not all the surfaces of the tablets were covered well. Thus, the drug release began almost at the beginning of dissolution. At a higher coat level (5% weight gain), when a dense, continuous, and fully coalesced film is formed which is relatively impervious in nature, greater resistance to media penetration shifted T-10 from less than 1 h for uncoated tablets to over 12 h. From these observations it was concluded that a coat of Surelease alone was not sufficient to achieve the goal of this project. Therefore, an alternative approach — inclusion of a channel-forming agent with Surelease — was followed.

When PEG was added with Surelease at a level of 20% or more, T-10, T-50 and T-90 reduced significantly (Table 2). Upon exposure to dissolution media PEG leached out of the film rapidly resulting in a highly porous membrane through which the drug diffused easily into the surrounding media. Typical pore formation under these conditions as viewed with a scanning electron microscope (SEM) is shown in Figure 1. When the total coat weight gain was high, the same level of PEG in the dispersions produced significantly lower drug release as compared with the one effected by lower weight gain (e.g. at 7.5% weight gain with 20% PEG in Surelease (formulation F) the observed T-50 was about 13.2 h, while at 5% weight gain with 20% PEG it was about 6.7 h (coat D)). Therefore, both the PEG level and the level of final coat weight gain are considerable factors in modulating the drug release. Besides its channel-forming action, PEG also works as a plasticizer in Surelease. It has been reported that PEG at the 20% level decreased the Tg of Surelease dispersion from 34.9˚C to 29˚C (Rohera & Parikh 2002). It is possible that PEG molecules diffuse into the polymeric network of

<table>
<thead>
<tr>
<th>Coat</th>
<th>CPD</th>
<th>SR</th>
<th>PEG in SR</th>
<th>T-10 (h)</th>
<th>T-50 (h)</th>
<th>T-90 (h)</th>
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<td>0.6 ± 0.2</td>
<td>2.3 ± 0.8</td>
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</tr>
<tr>
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<td>2.5</td>
<td>0.0</td>
<td>2.7 ± 1.6</td>
<td>9.2 ± 2.7</td>
<td>&gt;24</td>
</tr>
<tr>
<td>B</td>
<td>0.0</td>
<td>5.0</td>
<td>0.0</td>
<td>12.6 ± 0.8</td>
<td>&gt;24</td>
<td>&gt;24</td>
</tr>
<tr>
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<td>15.0</td>
<td>5.7 ± 1.7</td>
<td>16.4 ± 2.6</td>
<td>&gt;24</td>
</tr>
<tr>
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<td>20.0</td>
<td>3.2 ± 1.2</td>
<td>6.7 ± 1.1</td>
<td>10.3 ± 1.6</td>
</tr>
<tr>
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<td>5.0</td>
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</tr>
<tr>
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<td>5.2 ± 0.9</td>
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<tr>
<td>I</td>
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<td>5.8 ± 1.0</td>
<td>9.6 ± 1.8</td>
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<tr>
<td>J</td>
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<td>16.3 ± 1.8</td>
<td>&gt;24</td>
</tr>
<tr>
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<tr>
<td>R</td>
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<td>5.0</td>
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<td>7.9 ± 2.2</td>
<td>15.2 ± 1.4</td>
<td>19.2 ± 2.2</td>
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</tbody>
</table>

CPD, Aquacoat-CPD; SR, Surelease; PEG in SR, polyethylene glycol (%w/w) in Surelease. Data are presented as means ± s.d., n = 6.
ethylcellulose (Sakellariou et al. 1986), but at a higher level part of it remains outside the polymer network available for being dissolved by the media. As a result, the T-10 of all tablets coated with Surelease containing PEG lies between 2 and 3 h. These coating compositions alone are thus not effective in delivering the drug selectively to the distal small intestine and colon. Hence an enteric coating composition (CPD dispersions) was evaluated.

The time for 10% release (T-10) from the tablets coated with CPD at 2.5%, 5%, 7.5% and 10% weight gain (formulations G, H, I and J) were found to be about 0.9, 1.9, 2.7 and 3.2 h, respectively in the media of pH 6.8 (Table 2). Thus, CPD alone was not enough to predictably achieve the goals of this project, especially as far as the gastrointestinal physiological constraints were concerned. Under these circumstances two functional coats on the same tablets were applied and evaluated.

The tablets were subjected to an inner coat of different levels of CPD and an outer coat of 2.5% and 5% weight gain with Surelease containing 20% or 25% PEG (Table 2). When a 5% semi-permeable coat with channelling agents was applied on top of the 7.5% enteric coat, the T-10 was prolonged, increasing from 0.4 h to 8.4 h (uncoated tablets vs coat N). This was due to dissolution of the soluble channelling agent from the outer coat, and a limited amount of media coming into contact with the inner coat through the micropores. Limited availability of the media and poor hydrodynamics at the inner coat interface prolonged the dissolution and diffusion process of both the coat and the drug. Because of the gradual expansion of the core, hydrodynamics and mechanical stresses, the outer membrane eventually ruptured with loss of membrane integrity resulting in extensive exposure of inner interfaces and core to the dissolution media. The sigmoidal shape of the release profiles (Figure 2) obtained were also consistent with the physical transformation of the coated tablets in that the lag time, linear release and the tailing towards the end correspond to gradual dissolution of coat, rupturing, matrix-controlled release and final dissolution of core.

Formulations N and Q both have an inner coat of CPD at 7.5% and outer coat at 5% weight gain with Surelease containing 20% PEG in N and 25% PEG in Q. The T-10 and T-50 for N are 8.4 and 14.3, while for Q they are 7.3 and 12.4 h, respectively. At a higher level of channelling agents the film disintegrated and ruptured faster causing a more rapid drug release. A high concentration of PEG in the coating film prevents close packing of ethylcellulose, as the PEG solidifies between the polymeric droplets and particles during film formation. Therefore, the level of channelling agent needs to be carefully determined to achieve the objectives. From the above observations, the coating formulation N (T-10 and T-90 are 8.4 and 19.4 h, respectively) appears to be the most reasonable one for further characterization to achieve the goal of this project.

**Dissolution in the presence of pectinolytic enzyme (bio-relevant media)**

Since the dosage form is designed to deliver drug at different parts of the distal intestine and colon, reasonable dissolution test conditions should be developed accordingly. The ideal situation would be the reconstruction of the gastrointestinal environment in in-vitro tests. Besides the physicochemical nature of the drug and excipients, various gastrointestinal factors play critical roles in drug liberation from the dosage form. For example, volume, pH, enzymes, electrolytes, surfactants, total dissolution time and hydrodynamics can greatly influence the solubility and dissolution rate of a drug (Dressman et al. 1998; Jamzad & Fassihi 2006). An ideal bio-relevant media is, therefore, one that accommodates all of the determining factors.
In this study, bio-relevant dissolution media of three pH values with pectinolytic enzymes have been employed for evaluation of formulation N. The tablets were placed for the first 2 h of dissolution in pH 1.5, for the next 2 h in pH 5.5 and the remaining 20 h in pH 6.8 with pectinolytic enzymes. The coated formulation N (7.5% weight gain with CPD and the outer coat of 5% weight gain with Surelease containing 20% PEG) released about 10% and 90% of its contents in about 7.5 and 18 h (Figure 3). The level of pectin in the formulation of the core tablet was only 12.5%, which failed to produce a significant impact on the release rates in the presence of the enzyme. In addition, the matrix was not readily exposed to the enzymatic effects before shell rupturing. Nevertheless, the overall performance of the formulation satisfied the needs of this project (i.e. the onset of drug release is prolonged to about 6 h and almost 90% of the dose is released in about 18 h).

**Stability studies**

Tablets stored in a sealed bottle with or without desiccant did not exhibit significant difference in release profiles compared with the newly coated tablets, as shown by their $f_1$ and $f_2$ values (Table 3). However, storage under elevated temperature and humidity for 90 days resulted in faster release rates from the tablets. The release profiles of tablets stored at 75% relative humidity at 40˚C significantly differ from those of the newly coated tablets, as their $f_1$ was found to be higher than 50 and $f_2$ less than 50. Nevertheless, the tablets retained their enteric and controlled release properties. It is apparent that heat and humidity have adverse effects on the coatings in general. It has been reported that a high level of plasticizer in the film, together with moisture, often increases membrane permeability (O’Donnell & Mcginity 1997). Further understanding of these effects in general and more specifically in this work is a subject for further investigation.

**Conclusions**

A pH- and time-dependent colonic delivery system was developed by application of an outer semi-permeable coat with pore forming agents on top of an enteric coat on the tablet core. When the two functional coats were applied separately, desirable release profiles were not obtained. It is well recognized that the usual transit time to the colon is about 6 h, and ideally a delivery system should not begin releasing its contents until it reaches the ileocecal junction. When in-vitro evaluations were carried out, the dual-coated formulation did not release its contents in media of pH 1.5 or 5.5 for 12 h. However, it provided reproducible and controlled drug release in pH 6.8 with an initial lag time of about 6 h. The coating shells were generally ruptured at around 15 ± 2 h due to swelling of the matrix and hydrodynamics of the surroundings. The developed tablet formulation retained its enteric properties and time-dependent release characteristics throughout three months of storage at 40˚C/75% RH. Moreover, the tablets stored in a sealed container with desiccators exhibited reproducible and similar release profiles to those of the newly coated tablets. The developed delivery system, therefore, offers potential for a predictable onset of release with extended delivery in a controlled manner.

**Table 3** 90-day stability data from dissolution profiles of coating formulation N

<table>
<thead>
<tr>
<th>Storage conditions</th>
<th>T-10 (h)</th>
<th>T-50 (h)</th>
<th>T-90 (h)</th>
<th>$f_1$</th>
<th>$f_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly coated tablets</td>
<td>8.4 ± 1.1</td>
<td>14.3 ± 1.2</td>
<td>19.6 ± 1.4</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Silica in sealed bottle</td>
<td>8.1 ± 2.4</td>
<td>13.9 ± 2.6</td>
<td>18.4 ± 2.8</td>
<td>7.2</td>
<td>74.4</td>
</tr>
<tr>
<td>Sealed bottle</td>
<td>7.4 ± 2.6</td>
<td>13.4 ± 2.7</td>
<td>17.6 ± 2.9</td>
<td>19.4</td>
<td>58.2</td>
</tr>
<tr>
<td>40˚C/75% RH</td>
<td>6.6 ± 2.8</td>
<td>11.2 ± 2.8</td>
<td>16.3 ± 3.1</td>
<td>48.2</td>
<td>40.8</td>
</tr>
</tbody>
</table>

$f_1$, dissimilarity factor between profiles; $f_2$, similarity factor. Data are presented as means ± s.d., $n = 6$.

**References**


